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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,138	STOTT, KELVIN	
	Examiner	Art Unit	
	Samuel W. Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,41 and 45* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,41 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.00

DETAILED ACTION

Status of the claims

Claims 1-26, 41 and 45 are pending.

Applicants' amendment filed 5/12/05, which cancels claims 27-40 and 42-44, adds claim 45, and amends claims 1-26 has been entered. Also, the applicants' request (filed 5/3/05) for extension of time of one month has been entered. Thus, the pending claims 1-26, 41 and 45 are examined in this Office action.

Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn.

IDS

The references listed in the IDS filed 5/3/05 have been considered by Examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the invention as now claimed.

This is a new matter rejection for the following reasons:

The amended claim 1, item c) "an extended ribbon" and "the alternate edges of the ribbon" represent a departure from the specification and the claims as originally filed.

Applicant's amendment (page 32) asserts that no new matter has been introduced by the amended claims (see page 32, the first paragraph). However, the specification does not appear to provide a clear support for the "extended ribbon" and the "edges of the ribbon". The instant claims now recite limitations which were not clearly disclosed in the specification and claims as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Claim Rejections - 35 USC § 112, the second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-26, 41 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, item c), recites "*an extended ribbon having two edges, a first edge and a second edge*"; the recitation is unclear because the term "ribbon" has not been described/defined in the specification, the term "ribbon" refers to a ternary structural model of describing high order structure of protein. Does the edges of ribbon refer to (i) β-edges (see page 2754, the right column of *Richardson et al.* reference); or (ii) termini of a β ribbon; or (iii) faces of β ribbon

which are parallel to hydrogen bonding forming between two β-strands in said β ribbon, or, (iv) faces perpendicular to the face of (iii)?

Claim 1 is unclear in the term "*edge*"; the specification provides insufficient teaching for this term. Claim 1, item c), recites "*a first edge" and "a second edge*". The recitation is unclear as to which reference (e.g., a target β-strand with which the claimed β-strands-forming section interacts through the said edge) does the claimed peptide compound involve in and/or prevent β-sheet formation with the target β-strand?

Claim 1, item a), recites "*a β-strands-forming section of peptide*". the recitation is not apparent as to whether or not "peptide" is the same peptide which comprises the β-strands-forming section, or a peptide fragment consisting of four to sixteen consecutive α-D-amino acid residues".

Also, claim 1, item d) recitation "*the β-strand*" has no antecedent basis in the claim as the said "β-strand" is not considered to be the "β-strands-forming section" set forth in item a). See also claim 11.

Further, Claim 1 recites "*at least 50% of said peptide*"; the recitation is not apparent as to whether or not "50% of peptide" refers to 50% (amino acid) composition (not sequence) of the peptide, or 50% of length of the peptide.

All the claims depending from claim 1 are also rejected.

Claim 6 recitation "β-strands forming section" lacks antecedent basis in claim 1 from which claim 6 depends. Note that claim 1 recites "β-strands-forming section".

Claim 23 is not apparent in the recitation "a sequence of side chains" because the amino acid sequence is composed of amino acid residues but not side chains alone.

The applicants' response to the rejection under 35 USC 112, second paragraph

On page 37, the response foiled 5/12/05 argues that claim 23 recitation "*a sequence of side chains...*" is not indefinite as the claim has been amended so as to refer "*a sequence of side chains of amino acid residues...*" to a part of amino acid residues of the β-strand forming section of the peptide. The applicants' argument is found to be unpersuasive because the above-mentioned amendment does not render the claim definite. Note that the side chains *per se* cannot constitute a sequence.

The rejections under 35 USC 102(e) by Findeis et al. (US Pat. No. 6610658) is withdrawn. Findeis et al. do not expressly teach and/or provide working example for a peptide composition comprising a peptide that comprises a β-stand-forming section consisting of 4-6 consecutive α-D-amino acid residues wherein said β-stand-forming section comprised at least one Nα-substituted residue.

The following is the new ground(s) of rejection.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-26 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Findeis et al. (US Pat. No. 6610658).

Findeis et al. teach an β-amyloid modulatory compound comprising polypeptide which possesses β-stand-forming section that comprises at least six α-D-amino acid residues (see Formula III, columns 13-14) and preferably 3-10 α-D-amino acids (see column 9, line 18); said β-stand-forming section is derived from the β-strand-forming portion of β-amyloid peptide (Aβ) (see abstract and column 18, lines 7-24).

Also, Findeis et al. teach that flanking the above " " (Formula III) structure, the peptide further comprises peptidomimetic region (see column 18, lines 14-15); further, Findeis et al. teach that the peptidomimetic modification include peptide back-bone modification, e.g., N-alkyl substitution (see column 17,lines 31-47). Furthermore, Findeis et al. teach the said β-amyloid modulatory compound includes the peptidomimetic compound comprising one or more N-methyl peptide bond (i.e., Nα–substitution) to introduce additional steric hindrance to the aggregation of natural β-amyloid when the compounds interact with natural β-amyloid (see column 20, lines 56-60). The above Findies' teachings meet the structural limitation set forth in instant claim 1.

It is of note that claim 1 as written does not clearly define/describe the edges of the β-stand-forming section of the peptide (see the above rejection under 35 USC 112, second paragraph). Thus, the Findeis et al. teachings are applicable, and that the structural characteristics of the claimed compound will not be altered by how to define the structure but is determined by the structural limitation(s).

On column 20, lines 56-60, Findeis et al. teach that the Nα–substitution sterically hinders interaction of peptidomimetic compound with other β-strand, as applied to instant claim 4.

The above-mentioned Nα-methylation is an Nα-substituted with methylene (CH_2) group, the above Findeis' teaching is applied to the instant claim 5.

Since ability of α-D-amino acid and α-L-amino acid residues form of forming β-sheet conformation is inherent property of the residues, the above Findeis et al. teaching is applied to instant claim 6.

On columns 14-15, Findeis et al. teach that in the Formula III, Xaa1-5 are essentially hydrophobic amino acids, e.g., phenylalanine (see especially SEQ ID NOs:5-25 of column 15) that has β-sheet propensity ≥1.00, as applied to instant claims 7-9.

Findeis et al. teach that "Z" position in the above-mentioned Formula III, encompasses any D-amino acid(s) including Glu (the β-sheet propensity ~ 0.37), and thus, Glu is a β-sheet conformation breaker and would hinders stacking of β-strand, as applied to instant claim 10.

Allowing that said chain of one or more amino acids in the β-strand forming section extends beyond the neighboring side chain in the said section is an inherent property of the Findeis' peptidic compound, which is applied to instant claim 11.

Findeis et al. teach that the modulator compound (modulating amyloid peptide aggregation) is modified to label the compound with a detectable substance, e.g., a radioactive label, (see column 3, lines 50-52), which is applied to the instant claims 12-13.

Since the D-amino acid residues of the Findeis' peptidic compound are enantiomers of L-amino acids which are mirror image chemical isomers to D-amino acids thereof, the above Findeis' teachings are applied to instant claim14.

Findeis et al. teach that the target β-strands (natural β-amyloid) with which the Findeis' compound interacts is derived from Alzheimer' β-amyloid peptide of SEQ ID NO:1(see column 6, lines 41-60 and columns 1-2); the said SEQ ID NO:1 sequence comprises the instant SEQ ID NO:5 (KLVFFAE) (residues 20-26 of SEQ ID NO:1), which is applied to instant claims 15 and 25.

Findeis et al. teach that the core domain of a β-amyloid peptide (i.e., a target molecule) comprises amino acid residues 17-20 (i.e., LVFF) with which the Findeis' compound interacts (see column 10, lines 34-40), which meets the limitation set forth in the instant claim 16.

Findeis et al. teach that the said compound is chemically modified to form a prodrug with enhanced transmembrane transport wherein the modification includes a covalent linking of a fatty acid to the modulator (see column 29, lines 32-42), which is applied to the instant claim 17.

Findeis et al. further teach that modifying group can be coupled to a side chain of at least one D-amino acid residue of the peptidomimetic region flanking the core domain (e.g., through the epsilon amino group of a lysyl residue(s) (see column 18, lines 8-24), as applied to instant claim 18.

Findeis et al. teach that the β-strand-forming section of the compound has free N- and C-termini (see column 5, lines 40-45), which anticipates the instant claim 19.

Findeis et al. teach that the peptide composition is conjugated to a second peptide, i.e., forming a chimeric protein (see column 29, lines 45-51), as applied to instant claim 20.

Findeis et al. further teach the said conjugation between the peptide compound and prodrug peptide (the second peptide) is produced so as to enhance transport of the peptidomimetic

compound across blood-brain barrier (see column 25, the first paragraph), which is applied to the instant claim 21.

Findeis et al. teach that the mean for the conjugation is through carboxyl group of aspartic acid residue (see column 18, lines 8-17), as applied to instant claim 22.

On the formula III and column 15, Findeis et al. teach that the β-strand-forming section of the peptidic compound (see the sequences of SEQ ID NOs: 5-25, column 15) comprises at least five amino acids; these sequences are homologous to "FFVLK" (the instant SEQ ID NO:3); and the formula II reads on SEQ UD NO:5. Thus, the Findeis et al. teachings are applied to instant claim 23.

Since the target β-strand (e.g., natural β-amyloid peptide) with which the Findeis' compound interacts, comprises a peptidic sub-sequence of "KLVFF" (see column 6, lines 51-60 and the patent SEQ ID NO:1), the above Findeis' teachings anticipate the instant claim 24.

Findeis et al. teach that backbone of the said peptidomimetic compound is modified by CSNH (thioamide) which produces a backbone of -(C=S)-NH- (see column 17, lines 41-46), as applied to instant claim 26.

Also, Further, Findeis et al. teach a pharmaceutical composition comprising the above-mentioned modulator compound (see column 29, lines 22-32), which anticipates the instant claim 41.

Yet, Findeis et al. does not provide working examples and/or expressly teach the peptide compound having the structural characteristics set forth in instant claim 1, e.g., the β-strand-forming section of the compound thereof comprising at least one Nα-substituted amino acid

residue involving in interfering with association of the section with target β-strand containing molecule.

It would have been obvious to a person having ordinary skill in the art to make the above mentioned peptide compound that comprises β-strand-forming section having 4-32 α-D-amino acids and comprising at least one Nα-substituted residue within the section. One skilled in the art would have been motivated to do this because of the following reasons.

(1) The Findeis et al. peptidic compound is derived from core domain of natural β-amyloid (see column 25, lines 17-28) which typically consists of 3-6 residues (see the formula III and SEQ ID NOs:5-25 on column 15).

(2) Findeis et al. have taught that the peptidomimetic modification includes peptide back-bone modification, e.g., N-alkyl substitution (see column 17,lines 31-47), and that their β-amyloid modulatory compound includes the peptidomimetic compound comprising one or more N-methyl peptide bond (i.e., Nα–substitution) to introduce additional steric hindrance to the aggregation of natural β-amyloid when the compounds interact with natural β-amyloid (see column 20, lines 56-60).

(3) Furthermore, Findeis et al. have taught that the peptidomimetic modification region comprising the Nα–substituted residue(s) can be in flanking to the core domain thereof, which meets the structural limitation of the current claim 1.

Thus, one skilled in the art would have been motivated by the above Findeis' teachings and would have made the Findeis' peptidic compound comprising the D-amino acids thereof and additionally comprising the Nα–substituted residue(s) in order to scale up potency of said

compound in inhibition of β-amyloid aggregation thereby inhibit the neurotoxicity of natural β-amyloid (see "*Summary of the Invention*", column 2, lines 62-65).

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed

Prior Art

The prior art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

(1) Charlifour et al. (*J. Biol. Chem.* (2003) 278, 34874-34881) teach that D-form peptide comprising D-amino acids, which is derived from β-strand-forming core (e.g., D-KLVFFA peptide), has ability of form β-sheet conformation with target strand, e.g., D- or L- KLVFFA peptide (*see abstract and the circular dichroism spectroscopic profiles depicted in Figure 4*), and that the D-peptide is more potent inhibitor than L-peptide for inhibiting aggregation of βamyloid polypeptides.

(2) Janek et al. (*Biochemistry* (1999) 38, 8246-8252) teach that replacement of amino acids (two residues) in a water-soluble β-sheet influences (destabilizing effect) β-sheet conformation as shown by circular dichroism spectroscopy (Figure 2 and page 8249).

(3) Wiesehan et al. (*Chembiochem* (2003) 4, 748-753) show that D-peptide derived form natural β-amyloid (Aβ) comprising D-amino acids (i.e., D-enantiomeric Aβ) bind to Alzheimer's disease amyloid peptide $A\beta_{1-42}$.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.
AU1653, Patent Examiner
July 20, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER